THE DIAGNOSIS AND MANAGEMENT OF OPTIC NEURITIS

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INTRODUCTION
Optic neuritis is a general term that is used to describe inflammation of the optic nerve. Although a variety of infectious, ischemic, and autoimmune conditions are associated with optic neuritis, the most common form of the disease, acute demyelinating optic neuritis, is best known for its association with multiple sclerosis [1, 2, 3, 4, 5]. In fact, optic neuritis is the heralding event of multiple sclerosis (MS) in 20% of patients, and it occurs in 50% of patients at some point during the course of their disease [6, 7, 8]. When acute optic neuritis occurs as an isolated event, without other signs and symptoms of MS at the time of diagnosis, it is referred to as idiopathic or monofocal.

Acute demyelinating optic neuritis predominantly affects young patients, and is about three times more common in women than in men [1, 4, 5, 7, 9]. Among populations at high risk for MS, the incidence of acute monosymptomatic demyelinating optic neuritis is approximately 3/100,000 per year (compared with 1/100,000 per year in lower risk populations) [1, 2, 5, 10, 11, 12].

CLINICAL FEATURES
The Optic Neuritis Treatment Trial (ONTT), the largest and most comprehensive study of the optic neuritis patient population to date, has provided important data about the clinical presentation and course of acute demyelinating optic neuritis [1, 2, 3, 13-31]. This trial, which followed an initial cohort of 457 patients over fifteen years, examined the effect of corticosteroid therapy on visual outcomes. Optic neuritis characteristically presents with acute to subacute onset of eye pain and vision loss. Patients typically describe a periorbital/ocular pain that is worse with eye movement. A prominent symptom reported by greater than 90% of patients, the eye pain usually progresses over hours to days, concomitant with the onset of vision loss [2, 3].

The degree of visual acuity loss is variable, although severe vision loss is uncommon. In the placebo group of the ONTT, the median visual acuity was 20/60 at baseline, which subsequently improved to 20/25 by day 15 and to 20/20 by one month from onset of symptoms [19, 21]. Relative to losses in visual acuity, color perception deficits are typically more pronounced. Positive visual phenomena, including phosphenes and photopsias, are also common in optic neuritis, and were observed in 30% of patients in the ONTT [2, 3]. Of note, acute optic neuritis is most often unilateral in adults, although a bilateral presentation is common in children. Adults who present with bilateral simultaneous optic neuritis should undergo the appropriate workup to exclude atypical causes; however, it should be noted that a substantial proportion of these rare cases are, in fact, due to demyelinating disease [32].

On examination, a relative afferent pupillary defect is almost always present, provided that the optic neuritis is unilateral and asymmetric. The appearance of the optic nerve on funduscopy is normal in 2/3 of patients; this presentation is termed retrobulbar optic neuritis. Similarly, the macula and retina are typically normal at initial presentation. The presence of peripapillary hemorrhages or retinal exudates suggests alternate diagnoses of anterior ischemic optic neuritis (AION) or neuroretinitis (Table 1). Within 4-6 weeks after symptom onset, visible optic nerve pallor usually develops, representing atrophy of the optic nerve head and thinning of the surrounding retinal nerve fiber layer [33].

Visual field defects are commonly observed in patients with optic neuritis. Although central scotomas are common, almost any type of defect may be observed [18, 22-25]. Altitudinal defects are less commonly seen in optic neuritis and, in the setting of sudden vision loss and optic disc swelling, should raise concern for AION (Table 1).

Spontaneous resolution of symptoms almost always begins within 2-4 weeks, and visual prognosis is good in many patients, regardless of treatment [2, 3, 31]. At ten years follow-up, visual acuity was >20/40 in 92% of the affected eyes in ONTT patients [31]. Many patients, however, continue to describe subtle deficits in visual function, despite return to baseline acuity [26, 27]. Patients with a visual acuity of 20/50 or less at 1 month have an increased chance of having moderate to severe loss at 6 months [80]. Reductions in contrast sensitivity and low-contrast acuity are frequently observed, even in the setting of normal high-contrast visual acuity [20, 34].
fact, contrast sensitivity in the ONTT was the most sensitive clinical measure for demonstrating residual visual dysfunction after acute optic neuritis [17]. Patients with visual dysfunction that worsens beyond a two week period, or that does not begin to improve within four weeks, should be evaluated for an alternate diagnosis [2, 4, 5].

**DIAGNOSIS**

**Magnetic Resonance Imaging**

The diagnosis of optic neuritis is generally based upon clinical history and exam findings. Brain MRI scan is an important diagnostic adjunct because of its utility in predicting the risk of subsequently developing MS [29]. White matter lesions > 3 mm in diameter and ovoid in shape are highly suggestive of MS [16]. They are characteristically periventricular in location. The ONTT determined that the ten year cumulative risk of developing MS in all patients was 38%, and there were significant differences in groups delineated by MRI findings. Those with MRI lesions have nearly three-fold increase of developing MS. For this reason, it is recommended that all patients with monosymptomatic optic neuritis undergo an MRI of the brain (T2-weighted and T1-weighted gadolinium enhanced images). MRI scans of the orbit with fat-saturation are also useful to confirm characteristic optic nerve enhancement, and to exclude alternative etiologies in atypical cases. It has been proposed that the diagnosis of MS can be established with a single MRI scan if it shows lesions that are disseminated in space and time (evidence of both enhancing and non-enhancing lesions) [86]. In addition to MRI appearance, there are several other baseline characteristics that relate to a patient’s risk of developing MS. Among patients with normal MRI scans in the ONTT, male gender and the presence of optic disk swelling associated with a lower probability of developing MS (hazard 0.35, p=0.05 for male gender; hazard 0.41, p=.01 for disk swelling) [29]. Also notable is the observation that no patient with a normal baseline brain MRI and atypical clinical features of painless or severe visual loss (no light perception), severe optic nerve swelling, peripapillary hemorrhages, or retinal exudates developed MS in fifteen years of follow-up [79].

**Lumbar Puncture**

A lumbar puncture, used to detect oligoclonal bands in the cerebrospinal fluid (CSF), may be useful in the diagnosis of MS but is not typically needed to diagnose acute demyelinating optic neuritis. In the ONTT, the presence of oligoclonal bands was associated with the subsequent development of MS; however, these patients also tended to have an abnormal MRI at baseline, which was independently predictive of MS. The CSF study provided additional diagnostic information only when the brain MRI was normal [35]. A study of oligoclonal banding in CIS patients with normal baseline MR showed the 4 year risk of CDMS to be 4% in patients with negative oligoclonal bands while risk climbed to 23% with positive oligoclonal banding [36]. We recommend CSF studies only for atypical cases of optic neuritis in which an infectious or systemic inflammatory disorder is suspected, and for cases in which the MRI findings suggest unusual patterns of enhancement or brain abnormality.

**Visual Evoked Potentials**

Visual evoked potentials (VEPs), used to assess neural conduction in the afferent visual pathway, are not routinely indicated, but may be used in the diagnosis of acute optic neuritis. Patients typically demonstrate reduced amplitudes and increased latencies, which represent the conduction block caused by inflammation and demyelination interrupting the continuity of the optic nerve fibers [37]. Although greater than 65% of patients with optic neuritis have abnormal VEPs [38], this finding is nonspecific and occurs with any pathologic process that damages optic nerve integrity, such as nerve compression or infiltration. In some cases, VEPs may be helpful in the diagnosis of MS when other requirements for the McDonald criteria have not been fulfilled [39]. Furthermore, VEPs may be predictive of patients that are destined to permanent RNFL loss. In a recent study, VEP latency and color vision at the presentation of optic neuritis later predicted the retinal nerve fiber layer loss by optical coherence tomography [84].

The advent of multifocal VEP (mVEP), which measures conduction from multiple segments of the visual field (including the periphery) allows for a more complete assessment of optic nerve function than conventional VEP. A study of 64 patients with confirmed optic neuritis demonstrated abnormal mVEPs in 97.3% of affected eyes; specific abnormalities included decreased amplitudes in 96.0% and increased latencies in 68.4% [38]. Of note, both amplitudes and latencies were abnormal in 100% of patients with confirmed multiple sclerosis by McDonald criteria. Data from a related study indicate that mVEPs may have a future role in predicting progression to MS after an isolated episode of optic neuritis [40]. mVEP’s using a low contrast check paradigm may further enhance the sensitivity of this technology to detect optic nerve injury [85].

New Imaging Techniques: Diffusion-Tensor MRI and Optical Coherence Tomography

In addition to conventional MRI, diffusion-tensor MRI (DT-MRI) is an imaging modality that may be able to detect disruptions in white matter that occur with demyelination and axonal injury.

In one recent study, DT-MRI imaging of optic nerves with a history of optic neuritis demonstrated increased mean diffusivity and decreased fractional anisotropy compared with clinically unaffected contralateral eyes (p<0.001) and control eyes (p<0.001) [41]. These measures were significantly correlated with decreased VEP amplitudes (p=0.006), although it remains unclear whether DT-MRI parameters also correlate with measures of visual function [41, 42].

Originally developed to monitor patients with macular pathology, and glaucoma, optical coherence tomography (OCT) is now being recognized for its emerging role in patients with optic neuritis. The pathophysiology of optic neuritis is characterized by acute inflammation of the optic nerve with consequent loss of axons. Over time, degeneration results in thinning of the retinal nerve fiber layer (RNFL) comprised of ganglion cells axons that form optic nerve [33, 43, 44]. The advent of OCT has now made it possible to quantitatively and non-invasively assess axonal loss, and this technique has applications to both optic neuritis and MS. The OCT technology functions analogously to ultrasound, using the reflection of near infrared light (820 nm), instead of sound, to create two-dimensional, cross-sectional images of the retina.

OCT studies have confirmed reductions in RNFL thickness in eyes with a history of optic neuritis [7, 45, 46]. One study demonstrated thinning of the RNFL within 3-6 months of an acute episode of optic neuritis in 74% of patients [45]. Such reductions in RNFL thickness correlate with decreases in visual function, as represented by measures of high-contrast visual acuity, VF mean deviation, and color vision [47]. Greater reductions in RNFL also correlated with less complete visual recovery, suggesting that OCT may have utility in predicting persistent visual dysfunction following an episode of optic neuritis [45]. The time course of RNFL loss following a bout of acute optic neuritis has been determined. 99% of the RNFL loss after optic neuritis is complete by 6 months [84].

Several OCT studies have also supported the idea that subclinical axon loss and visual abnormalities occur in MS patients, even in eyes without a clinical history of acute optic neuritis [45-48]. Fisher, et al demonstrated that, among MS patients and disease-free controls, the greatest decreases in RNFL thickness occurred in eyes affected by optic neuritis; however, the unaffected eyes of MS patients also showed reductions in RNFL thickness, relative to disease-free controls (p=0.03) [48]. More recently, computerized programs have permitted the segmentation of the retina into various layers. This new technique permits examination of the ganglion cell layer allowing the assessment of neuronal loss in patients with multiple sclerosis. It is important to note that the ganglion cell- inner plexiform layer may start to shrink weeks after an episode of optic neuritis suggesting that the time to intervene after an acute episode can be narrow. Nonetheless, the capacity of OCT to identify subclinical axon loss and neuronal loss may facilitate early intervention and better long term visual outcomes [46, 49]. These data suggest that OCT may serve an important future role in monitoring patients with optic neuritis and MS, both clinically and in the setting of treatment trials.

THERAPY

Short Term Therapy

The current treatment of acute demyelinating optic neuritis has been largely influenced by the findings of The Optic Neuritis Treatment Trial (ONTT). The ONTT was a randomized, multicenter clinical trial of visual outcomes in patients with optic neuritis [1, 2, 3, 13, 14-15, 16, 17, 18-20, 21, 22-27, 28, 29, 30, 31]. The ONTT and its extension study (Longitudinal Optic Neuritis Study – LONS), which continues to follow the original cohort, have been important sources of information regarding baseline clinical features, long-term visual prognosis, vision-specific health-related quality of life, and role of brain MRI in determining the risk for subsequent development of clinically definite MS (defined as a second demyelinating event).

The primary objective of the ONTT was to determine the effect of intravenous and oral corticosteroid therapy on visual outcomes in acute demyelinating optic neuritis [1, 2, 3, 15, 18-20, 21, 31]. As a secondary aim, the ONTT evaluated the effect of corticosteroid treatment on the risk for developing MS [13, 14, 16, 17, 29]. The ONTT enrolled 457 patients, aged 18-46 years, with acute unilateral optic neuritis. These patients were randomized to one of three treatment groups: 1) oral prednisone (1 mg/kg/day; [50]) for 14 days with 4-day taper (20 mg on day 1, 10 mg on days 2 and 4); 2) intravenous (IV) methylprednisolone sodium succinate (250 mg every 6 hours for 3 days followed by oral prednisone (1 mg/kg/day) for 11 days with 4-day taper; or 3) oral placebo for 14 days [3**]. A baseline MRI scan of the brain was performed for each patient. Visual function, including measures of visual acuity, contrast sensitivity, visual fields, and color vision, was assessed at baseline and at various points in more than ten years of follow-up.

The findings of the ONTT continue to guide the treatment of optic neuritis today [1, 2, 3, 13, 14-15, 16, 17, 18-20, 21, 22-27, 28, 29, 30, 31]. Patients treated with IV methylprednisolone experienced faster recovery of visual function, particularly in the first fifteen days after onset of visual loss, than did patients in the oral...
prednisone and placebo groups. However, these differences decreased over time until, at one year follow-up, there were no significant differences in visual function between the treatment groups. Additionally, the ONTT demonstrated that treatment with oral prednisone did not affect recovery time. In fact, patients in the oral prednisone group experienced increased rate of recurrent optic neuritis in either eye (risk at 2 years was 30% vs. 13% in methylprednisolone group vs. 16% in placebo group). At ten years' follow-up, the recurrence risk remained higher in the oral prednisone group (44%) compared with the placebo (31%, p=0.07) and IV methylprednisolone groups (29%, p= 0.3), although these differences did not achieve the degree of significance observed for the 2-5 year data [31].

The ONTT secondary analyses examined the effect of treatment on the risk of developing MS after a first episode of optic neuritis, and related these findings to baseline MRI characteristics [13, 17, 29]. Within the first two years of follow-up, the risk of developing MS was significantly lower in the group treated with IV methylprednisolone (7.5%), than in the oral prednisone and placebo groups (14.7% and 16.7%, respectively). The presence of two or more white matter lesions on baseline MRI was strongly associated with the development of MS (p<0.001), and in this group of high risk patients, the protective effect of IV methylprednisolone was most apparent. It is important to note, however, that beyond two years of follow-up, there were no significant differences between treatment groups.

A similar randomized control trial in Japan published results consistent with those reported by the North American ONTT. The Japanese study demonstrated more rapid recovery of visual function for patients receiving IV methylprednisolone vs. a control drug (mecobalamin); however, there was no effect on long-term visual outcome [11, 12]. These results support the ONTT findings in a different patient population.

To summarize the findings from the ONTT and comparable trials, IV methylprednisolone, when given within 1-2 weeks of symptom onset, may speed recovery of visual function [1, 2, 3, 15, 18-20, 21, 31] and decrease the risk of MS within the first two years of follow-up, especially in patients considered to be at high risk by MRI criteria [13, 14, 16, 17, 29]. However, treatment with IV methylprednisolone has no proven effect on either long-term visual outcome or long-term risk of developing MS [21, 29, 31]. Treatment with oral prednisone alone may increase the short-term risk of recurrent optic neuritis and, for this reason, should be avoided. The role for high-dose oral corticosteroids in treating acute demyelinating optic neuritis has not yet been adequately studied. Based on these data, the most commonly used therapy for acute demyelinating optic neuritis is IV methylprednisolone (1 g/day for 3 days) followed by oral prednisone (1 mg/kg/day for 11 days followed by a 4-day taper).

Long-Term Therapy for Early MS

There have been several important studies that support the treatment of patients with optic neuritis and a positive MRI with immunomodulatory therapy. The Controlled High-Risk Avonex MS Prevention Study (CHAMPS), enrolled 383 patients with a recent history (within 14 days) of a demyelinating event, a large subset of which were patients with optic neuritis [51, 52, 53]. These patients also had brain MRI findings consistent with high risk for clinically definite MS as established by the ONTT (>2 white matter lesions, ≥ 3 mm in diameter, at least 1 lesion periventricular or ovoid; Grade 3 or 4 MRI by ONTT criteria [16]). Patients randomized to the treatment group received weekly intramuscular injections of 30 µg interferon beta-1a[50]). Results demonstrated a reduced 3-year cumulative probability of clinically definite MS in the treatment group compared with placebo (0.50% vs. 35% for placebo; p= 0.002). In addition, these patients showed a reduced rate of accumulation of new but clinically silent lesions on brain MRI (p < 0.001 for new and enlarging T2 lesions at 18 months).

An extension of the CHAMPS study, the Controlled High Risk Avonex MS Prevention Study in Ongoing Neurologic Surveillance (CHAMPIONS), aimed to demonstrate whether immediate treatment with interferon beta-1a following a first demyelinating event is more effective in controlling disease activity and disability than delayed treatment [54]. The CHAMPIONS trial was an open-label extension study that enrolled 53% of the patients participating in CHAMPS. This cohort was divided into an “immediate treatment” (IT) group, who had received interferon beta-1a immediately after the first symptomatic event, and a “delayed treatment” (DT) group, who had received placebo during CHAMPS, but was subsequently started on interferon beta-1a at a median of 2.5 years after the first demyelinating event. Results at five years showed that the probability of developing clinically definite MS was lower in the IT group than the DT group (unadjusted hazard ratio 0.65, p=0.03). When adjusted for age, sex, and baseline MRI, the reduction of MS risk in the IT group was slightly more robust (adjusted hazard ratio 0.57, p=0.008). The study also suggested that there may be a modest reduction in disease activity, as measured by number of new or enlarging MRI lesions, in patients beginning treatment with interferon beta-1a immediately after symptom onset. More recently, the ten year data from the Champions study has been reported and the benefits of early treatment remain evident [81]. It is important to note, however, that unlike the CHAMPS...
study, CHAMPIONS was an open-label trial, and did not include the entire intent-to-treat study cohort. The CHAMPIONS study concluded that the benefits observed in CHAMPS were sustained at ten years, as the probability of developing clinically definite MS remained significantly reduced in the IT group.

The Early Treatment of MS (ETOMS) Study Group also yielded results that demonstrated a benefit for interferon beta-1a treatment following a first clinical demyelinating event such as optic neuritis [55]. Patients with both neurologic and radiologic evidence of a first demyelinating event were randomized to weekly injections of subcutaneous interferon beta-1a 22 µg [50]) or placebo within three months of symptoms and were monitored over a two year period. Comparable to the findings of the previous interferon beta-1a trials, ETOMS found a lower risk of developing clinically definite MS (34% vs. 45%, p=0.047), as well as a lower annual relapse rate (0.33 vs. 0.43, p=0.045) in the treatment group compared to placebo. Disease activity, as measured by lesion burden on MRI, was also significantly lower. In a related study of the same cohort, patients receiving interferon beta-1a demonstrated a reduced rate of brain volume loss over two years (-1.18% vs. -1.68% in placebo group, p<0.0001), suggesting that early treatment with interferon beta-1a may have the additional benefit of slowing the progressive loss of brain parenchyma that is frequently seen in patients with MS [56].

The Betaferon in Newly Emerging MS for Initial Treatment (BENEFIT) Study, a randomized, placebo-controlled phase III trial demonstrated that treatment with interferon beta-1b delays the development of clinically definite MS was 28% in the treatment group, compared to 45% in the placebo group (hazard ratio= 0.50, p<0.0001). Risk for developing MS as defined by the McDonald criteria was reduced from 85% to 69% (hazard ratio= 0.54, p<0.0001). Secondary efficacy variables, which reflect the burden of inflammatory lesions on MRI scan, also demonstrated positive treatment effects.

The PRECISE trial confirmed the benefit of Glatiramer acetate in the treatment of the patient with the clinically isolated syndrome. There was 45% reduction in the conversion to CDMS favoring those treated with Glatiramer acetate.[82] A positive effect was also on the imaging outcomes including T2 abnormalities and gadolinium enhancement. Although not formally tested in the clinically isolated syndrome patient, the emergence of oral therapies for the treatment of MS gives the patient in the earliest phases of the disease new therapeutic options. Oral therapies are being used much more frequently in the earlier stages of the disease even after a single scan suggests the diagnosis of MS or places the patient in a high risk category.

With the advent of long-term therapy options, it is reasonable to consider whether it is necessary or beneficial to begin indefinite therapy for a chronic disease with a variable natural course. Some physicians advocate an initial observation period to better determine the patient's disease progression before initiating therapy [58]. They argue that many patients could avoid long-term therapy—and the financial expense and adverse effects that accompany it—without affecting the patient's prognosis. Other physicians argue that we cannot consistently identify such patients, and that we may risk long-term, irreversible disability by delaying treatment [59, 83]. Until we can reliably determine which patients can safely defer treatment, we recommend offering long-term therapy to all patients with a first demyelinating event when the MRI suggests high risk for MS. This therapeutic approach has become the rule rather than the exception. When the initial MR scan supports the diagnosis of MS, we would strongly advocate the initiation of long term therapy which now include a variety of oral therapies.

Other Therapy

Plasma exchange, used successfully in other inflammatory and demyelinating disorders, may have a role in treating optic neuritis patients who are unresponsive to other therapies. In a retrospective review of ten patients with steroid-refractory optic neuritis, plasma exchange was associated with short-term improvement in visual acuity in seven of these patients [60]. A large prospective controlled trial is necessary to better understand the role of plasma exchange in this unique patient population.

Small studies have suggested that intravenous immunoglobulin [50]) may have some benefit in patients with substantial visual deficits following optic neuritis [61]. However, subsequent randomized trials in which the outcome measure was either visual acuity or contrast sensitivity failed to demonstrate a significant benefit [62, 63]. Exploratory analyses in one study did suggest that IVIg may improve other measures of visual function, including visual fields and visual evoked responses [63]. The authors concluded, based on the available data, that IVIg administration does not reverse persistent visual loss from optic neuritis to a degree that merits general use. A more recent randomized trial, however, reported that treatment with IVIg during a first demyelinating event reduces both the one-year probability of progression to clinically definite MS, as well as disease activity as measured by MRI [66]. A larger study with longer patient follow-up is needed to better evaluate the effects of IVIg on MS risk. In addition, it should be noted that, despite these encouraging results, the practical use of IVIg remains limited by cost and availability.

PEDIATRIC CONSIDERATIONS

Acute optic neuritis in children characteristically has a different presentation than the typical adult form. One of the more striking differences is the severity of visual loss in pediatric optic neuritis. While adults tend to present with modest visual acuity deficits (median visual acuity of 20/60, as reported by the ONTT [19]), children commonly experience loss of visual acuity to 20/200 or worse [65-67]. In addition, past reports have suggested that visual loss in the pediatric population is more frequently bilateral, and more often associated with optic disk swelling. Despite this severe presentation, recovery of visual acuity in children, as in adults, is to the level of 20/40 or better on average.

Treatment of optic neuritis in children has not been studied with randomized trials and is instead based on established therapy for adults. Liu, et al, recommend intravenous methylprednisolone (4 mg/kg every 6 hours for 3-5 days) as the initial therapy if visual loss is bilateral, or if unilateral and severe, followed by an oral prednisone taper (starting at 1 mg/kg, then reducing dose over 2-4 weeks) [4]. For children with optic neuritis and abnormalities on brain MRI, interferons represent one potential treatment option. Evaluation of CSF and serologies is also recommended to exclude non-idiopathic causes of optic neuritis in pediatric patients [4].

As in adults, optic neuritis is frequently the first clinical sign of MS in children, although this risk is still not well defined. In a longitudinal study of 79 patients, the ten year risk of developing clinically definite or laboratory-supported MS after an episode of childhood optic neuritis was 13% [66]. At twenty years, the risk had increased to 19%. By comparison, the ten year risk of MS in adults, as reported by the ONTT, was considerably higher (38%) for all patients after an isolated first episode of optic neuritis [29].

In a retrospective study of 36 children (mean age at diagnosis = 12.2 years) optic neuritis was more frequently unilateral (58%), contrary to previous reports [67]. The proportion that developed MS in this cohort was higher than previously reported, with 13 children (36%) diagnosed with MS after a mean follow-up of 2.4 years (0.3-8.3 years). All 13 of these children had brain lesions separate from the optic nerve at their initial presentation. The presence of white matter lesions was associated with a subsequent diagnosis of MS (p<0.0001), and bilateral optic neuritis was more often associated with MS than unilateral optic neuritis (58% vs. 38%, p=0.03). Severe visual deficits at onset and age of first optic neuritis were not associated with risk of developing MS. Collectively, studies of pediatric optic neuritis indicate that large prospective studies are needed to further establish the clinical and neuroimaging profiles and MS risk in this population.

NEUROMYELITIS OPTICA

Among patients with recurrent demyelinating optic neuritis, a small subset does not fit the classic clinical or radiologic picture of MS. Many such patients are diagnosed with neuromyelitis optica (NMO), also known as Devic's disease. NMO is classically described as a severe demyelinating disease that preferentially targets the optic nerves and spinal cord; however, more recent observations suggest that some patients may have a more benign course resembling that of MS [68]. Patients typically present with acute onset optic neuritis, closely preceded or followed by paraparesis or paraplegia [37]. In contrast to typical demyelinating optic neuritis, the vision loss observed in NMO is often bilateral and severe, occasionally progressing to blindness. Some patients may suffer from frequent recurrent episodes of optic neuritis. Periorbital pain, an almost universal feature in typical demyelinating optic neuritis, is not as common in NMO[88]. The optic disk may appear normal or swollen, and varying degrees of visual recovery can occur.

MRI imaging typically demonstrates scattered areas of demyelination, concentrated in the optic nerves, chiasm, and spinal cord. Lesions of the spinal cord are longitudinally extensive, involving at least three vertebral segments [69]. Although NMO diagnostic criteria originally excluded patients with brain lesions on MRI, it is now believed that brain lesions may be seen in as many as 60% of NMO patients [70]; however, these lesions are typically nonspecific, and only about 10% resemble the typical MS morphology [69, 70]. There are now recognized variants of NMO which include patients with tumoralactive lesions, lesions concentrated in the thalamus and hypothalamus and lesions that are concentrated around the ventricles. Some of these presentations may precede the onset of visual loss.

A serum IgG autoantibody is associated with NMO, with a sensitivity in the 70% range and specificity of 90% [71, 72]. The antibody targets an aquaporin channel, located in the astrocytic foot processes of the blood brain barrier. The channel functions in fluid homeostasis.

There are no clinical trials that dictate the management of the patient with optic neuritis and a positive NMO titer. For acute therapy, I would suggest intravenous methylprednisolone 1 gram for 3 to 5 days followed by an oral taper. If there is minimal response to corticosteroid therapy and vision remains less than 20/200, I would advocate a course of plasma exchange for a total of 3 to 5 exchanges. For patients unable to tolerate plasma exchange, one could use gamma globulin [87]. For chronic therapy of NMO, I would start the patient on azathioprine or mycophenolate mofetil.[73, 74] I usually start azathioprine because it is less expensive. Rituximab is another excellent option for chronic therapy, but it can be occasionally difficult to get it approved by some

insurance companies for the treatment of NMO [75]. Anti-myelin oligodendrocyte glycoprotein (anti-MOG) is an antibody that may be present in those patients who are NMO negative but have an NMO phenotype. Also the anti-MOG antibody may be a marker of some cases of ADEM and in patients with recurrent optic neuritis.

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* papers of importance

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The Optic Neuritis Treatment Trial (ONTT) represents the largest and most comprehensive study to date on the treatment of acute demyelinating optic neuritis. This article reports the results of the primary ONTT analysis of visual outcome among patients randomized to IV methylprednisolone/oral prednisone, oral prednisone alone, or oral placebo.


13. * Beck RW, Cleary PA, Trobe JD, et al.: The effect of corticosteroids for acute optic neuritis on the subsequent development of MS. N Engl J Med 329, 1764-1769 (1993). This article reports that the development of clinically definite MS, a secondary outcome in the ONTT, occurred in 7.5% of the IV methylprednisolone group, compared with 14.7% and 16.7% of the oral prednisone and placebo groups, respectively, within the first two years of follow-up.


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17. ** Optic Neuritis Study Group: The five-year risk of MS after optic neuritis: experience of the Optic Neuritis Treatment Trial. Neurology 49, 1404-1413 (1997). The Optic Neuritis Study Group found the cumulative probability of clinically definite MS (30%) was similar.
across all treatment groups at five years follow-up. However, they reported that baseline MRI was a powerful predictor of MS risk at 5 years: 51% for patients with ≥ 3 white matter lesions, 37% for 1-2 matter lesions, 16% for 0 lesions.


Visual outcome data from the Optic Neuritis Treatment Trial cohort at 5 years demonstrated no significant differences in visual function test scores across treatment groups; however, the cumulative probability of recurrent optic neuritis in either eye remained significantly higher in the oral prednisone group (41%) compared with the IV methylprednisolone and placebo groups (25% for both groups).


This article summarizes the results of a mail survey of 900 neurologists and 987 ophthalmologists to evaluate whether practice patterns have been affected by results of the ONTT, and how specific recommendations have been interpreted. Although 95% of neurologists and 90% of ophthalmologists reported reductions in their use of oral prednisone (suggesting correct interpretation of ONTT results), a high percentage of respondents in both groups (38% of ophthalmologists, 59% of neurologists) reported using IV methylprednisolone for “improving 1-year visual outcome” (illustrating that trial recommendations may be implemented without a complete understanding of results).

29. ** Beck RW, Trobe JD, Moke PS, et al. High- and low-risk profiles for the development of MS within 10 years after optic neuritis. Arch Ophthalmol 121, 944-949 (2003). The Optic Neuritis Study Group reported that the 10-year risk of MS following an initial episode of acute optic neuritis is significantly higher in patients with one or more lesions on brain MRI at baseline, compared to patients with normal MRI scans (56% vs. 22%; p<.001).


Visual outcome data from the Optic Neuritis Treatment Trial cohort at 10 years demonstrated no significant differences in visual function test scores across treatment groups. However, the cumulative probability of recurrent optic neuritis in either eye remained higher in the oral prednisone group (44%) compared with the IV methylprednisolone (29%, p= 0.3) and placebo groups (31%, p=0.07).


This article describes a randomized trial of low-dose interferon beta-1a (Rebif), which demonstrated the efficacy of interferon beta-1a vs. placebo in reducing the risk of MS (34% vs. 45%; p=0.047), and in reducing number of new lesions on MRI at two years follow-up.

Predictors of visual outcome: nonarteritic anterior ischemic optic neuropathy (NAION) is distinguished from other types of optic neuropathies. The BENEFIT study demonstrated that, in patients with a first clinical demyelinating event and at least two clinically silent brain MRI lesions, treatment with interferon beta-1a delayed the development of MS, as defined by both the Poser and McDonald criteria (p<0.0001 and p<0.00001, respectively).

Not every patient with multiple sclerosis should be treated at the time of diagnosis. Treatment in acute optic neuritis.

Most patients with multiple sclerosis or a clinically isolated demyelinating syndrome should be treated at the time of diagnosis.

Most patients with multiple sclerosis or a clinically isolated demyelinating syndrome should be treated at the time of diagnosis.

Plasma exchange for severe optic neuritis.
84. Henderson A Altmann DR, Trip TS et al. A serial study of retinal changes following optic neuritis with sample size estimates for acute neuroprotection trials. Brain 133(9):2592-602, 2010
85. Frohman AR, Schnurman Z, Conger A et al. Multifocal visual evoked potentials are influenced by variable contrast stimulation in MS. Neurology. 79(8):797-801, 2012
Table 1. Clinical Features and Main Differential Diagnosis for Acute Demyelinating Optic Neuritis

<table>
<thead>
<tr>
<th></th>
<th>Acute Demyelinating Optic Neuritis*</th>
<th>Anterior Ischemic Optic Neuropathy (AION)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, sex</td>
<td>20-50 years, typically women (3:1)</td>
<td>&gt;50 years, men or women</td>
</tr>
<tr>
<td>Pain</td>
<td>Present in more than 90%, exacerbated by eye movement, resolves within 1 week</td>
<td>Uncommon (less than 10 %); headache occurs in temporal arteritis</td>
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<tr>
<td>Pattern of visual loss</td>
<td>Progression over hours to days, 7 to 10 days maximum**; unilateral in adult patients; signs of optic neuropathy (visual acuity, color vision, and visual field defects) §</td>
<td>Sudden onset, often noted upon awakening; unilateral in adult patients; signs of optic neuropathy (visual acuity, color vision, and visual field defects)</td>
</tr>
<tr>
<td>Optic Disc Appearance</td>
<td>Optic disc swelling in 1/3 of patients, retrobulbar in remainder, absence of hemorrhages/exudates†§</td>
<td>Optic disc swelling, sectoral involvement, hemorrhages, fellow eye disc crowded with small or no cup</td>
</tr>
<tr>
<td>Visual Field Defects</td>
<td>Typically central, but may be arcuate (radiate from physiologic blind spot), cecocentral (involve central vision and physiologic blind spot), hemianopic (involve area to right or left of vertical)</td>
<td>Typically altitudinal (involve area above or below horizontal)</td>
</tr>
<tr>
<td>Pattern of visual recovery</td>
<td>Begins within 2 to 4 weeks, generally favorable overall (20/20 or better in 75 percent with baseline normal vision)</td>
<td>Modest improvement over months in approximately 40 percent (by 3 lines or more on Snellen chart)‡</td>
</tr>
</tbody>
</table>

* Absence of these typical features should suggest other causes of inflammatory optic neuropathy or alternative diagnoses such as sarcoidosis, systemic lupus and other vasculitides, paraneoplastic disease, syphilis, Lyme disease, and Bartonella henselae infection (associated with cat scratch neuroretinitis), ischemic optic neuropathy, or Leber’s hereditary optic neuropathy. 6,7, 10, 43, 77, 78
† These ophthalmoscopic findings were associated with an extremely low (or zero) risk of developing MS by 10 years’ follow-up in the Optic Neuritis Treatment Trial (ONTT). 29**
‡ Ischemic Optic Neuropathy Decompression Trial (IONDT) data. 78
§ Optic neuritis in pediatric patients is more frequently bilateral, and is associated with optic disc swelling more commonly than in adults. 4,65,66
** The time course of symptom onset distinguishes demyelinating optic neuritis from other inflammatory or compressive optic neuropathies in which visual function may worsen relentlessly over weeks to months (such as sarcoid, meningioma, or pituitary adenoma).